

Testosterone Therapy Among Prostate Cancer Survivors

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ABSTRACT

Introduction: The use of testosterone in men with a history of prostate cancer remains controversial in light of established findings linking androgens to prostate cancer growth. However, hypogonadism significantly affects quality of life and has negative sequelae, and the risks and benefits of testosterone therapy might be worthwhile to consider in all men, even those with a history of high-risk prostate cancer.

Aim: To discuss the effects of testosterone on the prostate and the use of testosterone therapy in hypogonadal men with a history of prostate cancer.

Methods: Review of the literature examining the effects of testosterone on the prostate and the efficacy and safety of exogenous testosterone in men with a history of prostate cancer.

Main Outcome Measures: Summary of effects of exogenous and endogenous testosterone on prostate tissue in vitro and in vivo, with a focus on effects in men with a history of prostate cancer.

Results: Testosterone therapy ameliorates the symptoms of hypogonadism, decreases the risk for its negative sequelae, and can significantly improve quality of life. Recent studies do not support an increased risk for de novo prostate cancer, progression of the disease, or biochemical recurrence in hypogonadal men with a history of non-high-risk prostate cancer treated with testosterone therapy. Evidence supporting the use of testosterone in the setting of high-risk prostate cancer is less clear.

Conclusion: Despite the historical reluctance toward the use of testosterone therapy in men with a history of prostate cancer, modern evidence suggests that testosterone replacement is a safe and effective treatment option for hypogonadal men with non-high-risk prostate cancer. Additional work to definitively demonstrate the efficacy and safety of testosterone therapy in men with prostate cancer is needed, and persistent vigilance and surveillance of treated men remains necessary.

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Key Words: Hypogonadism; Testosterone; Hormone Replacement; Prostate Cancer; Prostatectomy; Radiation Therapy

INTRODUCTION

Hypogonadism is newly diagnosed in approximately 500,000 men annually and is characterized by decreased serum testosterone levels. Hypogonadal men can experience signs and symptoms such as impaired sexual function, decreased muscle mass and strength, decreased bone mineral density, decreased cognition, and depressive symptoms.^{1,2} Hypogonadism affects

5.6% of men 30 to 79 years old and 18.4% of men older than 70 years and increases in incidence with age; no difference in prevalence by race or ethnic group has been observed.^{3–5} This older population also is frequently affected by prostate cancer, which accounts for one in five new cancer diagnoses.⁶ However, prostate cancer mortality has decreased 50% during the past two decades as a result of improvements in early detection and treatment. As a result, more patients are living with a history of prostate cancer. The aging of the U.S. male population and the growing population of prostate cancer survivors have resulted in a significant increase in the number of men reaching older age, thus increasing the likelihood of hypogonadism in these men.

From 2001 to 2011, androgen use in men older than 40 years increased more than threefold with its ability to treat the symptoms of hypogonadism (50.6%), fatigue (34.5%), erectile dysfunction (31.9%), and psychosexual dysfunction (11.8%).⁷ Long-term testosterone therapy also has been found to

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significantly increase trabecular and cortical bone mineral density, which is significant in light of the high frequency (20–50%) of hypogonadal testosterone levels in men with symptomatic vertebral fractures and hip fractures.^{8,9} Current evidence also supports the notion that testosterone acts as an immunomodulatory and atheroprotective hormone.¹⁰ As such, testosterone therapy has been associated with decreased mortality and improvement of cardiovascular risk factors, including fat mass and glycemic control.¹¹ However, controversy regarding the use of exogenous testosterone and associated cardiovascular risk remains, with numerous studies during the past decade supporting and refuting an association between testosterone use and increased cardiovascular risk.¹² Additional concerns initially arose after reports of increased cardiovascular risks associated with testosterone prescriptions.^{13,14} These claims are based largely on two flawed studies but have raised the profile of these concerns. In contrast, several dozen articles have suggested that testosterone deficiency actually decreases cardiovascular risk (reviewed by Morgentaler et al¹¹).

In the setting of prostate cancer, testosterone therapy use has been historically controversial owing to concerns raised by a landmark study that linked administration of exogenous testosterone to stimulation of prostate cancer growth.¹⁵ In 1941, Huggins and Hodges¹⁵ established a direct relation between prostate cancer and androgens. Their androgen-dependent model of prostate cancer growth was based on the observation that bilateral orchiectomy of eight men in their cohort and estrogen injections in another five men resulted in a marked decrease in serum acid phosphatase, a serum marker for prostate cancer that has since been replaced by prostate-specific antigen (PSA). In addition, they found that testosterone injections in three men resulted in marked increases in serum acid phosphatase and concluded that androgen injections stimulated prostate cancer growth. However, recent evidence does not support these early findings and in fact argues against them. The first study to observe a link between an increased risk of prostate cancer and low serum testosterone levels was published by Morgentaler et al¹⁶ in 1996 and identified prostate cancer in 14% of 77 men with low serum testosterone levels (Table 1). The significant impact that hypogonadism has on quality of life and the need to treat a growing population of men, many of whom will have prostate cancer during their lives, demonstrate a need for higher-quality evidence evaluating the safety and efficacy of testosterone therapy in these men. In this review, we examine the evidence for testosterone's effect on the prostate, focusing on endogenous and exogenous testosterone and normal and malignant prostate tissue.

METHODS

A review of literature was performed using the PubMed database to identify English-language studies and review articles related to data on testosterone replacement therapy and prostate cancer. An

analysis of the historical perspective was conducted, and study findings from 1994 to the present were considered. The seminal 1941 study by Huggins and Hodges¹⁵ was included.

MAIN OUTCOME MEASURES

Based on the literature, the effects of exogenous and endogenous testosterone on prostate tissue in vitro and in vivo were summarized, with a focus on effects in men with a history of prostate cancer.

RELATION BETWEEN ENDOGENOUS TESTOSTERONE LEVELS AND PROSTATE CANCER

Low Serum Testosterone

Available evidence supports an increased risk of prostate cancer in men with low serum testosterone levels, with studies observing higher rates of prostate cancer incidence, higher-grade disease, and higher likelihood of extraprostatic extension, biochemical recurrence (BCR), and positive surgical margins.¹⁷ Morgentaler et al¹⁶ suggested a possible relation between low testosterone and increased risk of prostate cancer in their study of 77 men with low total or free testosterone levels, normal digital rectal examination results, and PSA levels no higher than 4.0 ng/mL. They identified a high prevalence of biopsy-detectable prostate cancer in these men (11 men, 14%), despite their normal PSA levels. A prospective study of 206 men (103 with benign prostatic hyperplasia [BPH] and 103 with prostate cancer) found that lower testosterone levels correlated with a higher probability of finding advanced prostate cancer.¹⁸ A study of 568 patients who underwent prostate biopsy examination found that men with low testosterone levels (<3.85 ng/mL) had a significantly higher incidence of prostate cancer than men in the high testosterone group (≥ 3.85 ng/mL; 38.0% vs 29.5%, $P = .018$).¹⁹ A prostate cancer screening program used in 718 men investigated whether serum testosterone could serve as an adjunct test to validate PSA-weighted risk of prostate cancer in the “gray” diagnostic area (PSA = 3.0–<10.0 ng/mL).²⁰ The investigators found that men with modestly increased PSA level (<10.0 ng/mL) and low total testosterone level (mean = 3.6 ng/mL) were at increased risk for prostate cancer. A retrospective analysis of 345 hypogonadal men with a PSA level no higher than 4.0 ng/mL observed that prostate cancer was detected in more men with a testosterone level lower than 250 ng/dL compared with those with a testosterone level higher than 250 ng/dL (21% vs 12%, respectively).²¹

Low serum testosterone levels also correlate with more aggressive prostate cancer. Hoffman et al²² examined 117 men and observed that those with low free testosterone levels (≤ 1.5 ng/dL) had more extensive prostate cancer, based on a higher frequency of positive biopsy results (43% vs 22%, $P = .013$) and more high-grade tumors with a Gleason sum of at least 8 (7 of 64 vs 0 of 48, $P = .025$) than men with normal free testosterone levels (> 1.5 ng/dL). García-Cruz et al²³ found

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